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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,477	LORINCZ ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/13/2003, 10/22/2003, and 1/4/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0603*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This action is in response to the Response and Declaration under 37 CFR 1.132 filed June 13, 2003, to the Response to Notice of Non-Responsiveness filed October 22, 2003, and to the Response to Notice of Non-Compliant Amendment filed January 4, 2004. Claims 8-12 are now pending and under consideration. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statement filed June 13, 2003 fails to comply with 37 CFR 1.97(c) because it lacks a statement as specified in 37 CFR 1.97(e). Particularly, it is noted that the IDS indicates in paragraph 5 (page 2) that no fee is due and that the IDS is accompanied by "one of the certifications pursuant to 37 C.F.R. 1.97(e) set forth in paragraph 9 below." However, neither box in paragraph 9 has been checked; accordingly, the IDS does not in fact include either of the certifications set forth in 37 CFR 1.97(e). The IDS has been placed in the application file, but the information referred to therein has not been considered. With regard to foreign patent document 4445769CL, it is also noted that while Applicant has indicated (on page 1, paragraph 1 of the IDS) that "an English language translation of that item or a portion thereof or a concise explanation of the relevance of that item is enclosed," no such translation or

explanation has been provided. While Applicant indicates in the Response of June 13, 2003 that a "corresponding English language patent" U.S. patent 5,786,337, which "claims priority to" the German patent has been provided, it is noted that MPEP 609 A(3) states that an "English-language equivalent application may be submitted to fulfill this requirement [for a translation] if it is, in fact, a translation of a foreign language application being listed in an information disclosure statement." While there is no requirement that a translation be verified, Applicant has not in fact indicated whether the '337 patent is in fact a translation of the German patent (or, e.g., a translation of a portion thereof), and it is not known to the examiner whether these two applications have identical or different content. Accordingly, should Applicant chose to resubmit the IDS in a manner compliant with 37 CFR 1.97, Applicant should further indicate the relationship between the '337 patent and the German application.

Specification

THE FOLLOWING ARE NEW GROUNDS OF OBJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

4. The amendment filed June 13, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: on page 23, at line 14, the insertion of the language "isolated and," and on page 23, at line 20, the insertion of the language "to calibrators and cellular RNA." Regarding line 14, the specification has been amended so as to recite that "total RNA was isolated and purified" whereas it

previously recited "total RNA was purified." The insertion of the language "isolated and" indicates an additional action/step taken in RNA processing for which basis was not provided in the originally filed specification, and therefore constitutes new matter. Regarding line 20, while the specification previously indicated that probe mix was "added and hybridized" to "RNA specimens" earlier referred to as "Aliquots of cellular RNA," the specification as amended indicates that probe mix was added and hybridized to both cellular RNA and "calibrators." As the originally filed specification did not specifically refer to these steps being taken with the "calibrators," this amendment also introduces new matter. While it is noted that Applicant indicated in the Response of June 13, 2003 that the specification was "amended for clarification or to correct typographical errors" and that "No new matter has been added," Applicant did not identify any areas in the specification that provide basis for the instant amendments, and the amendments add new matter for the reasons stated above.

Applicant is required to cancel the new matter in the reply to this Office Action.

Declaration under 37 CFR 1.132

5. The Declaration under 37 CFR 1.132 filed June 13, 2003 fails to conform with the formal requirements for declarations and therefore cannot be considered. Specifically, the Declaration is defective because while it includes a statement that "all statements made on information and belief are believed to be true," it does not include a statement that all statements made of the declarant's own knowledge are true, as required by 37 CFR 1.68 (see also *MPEP* 715.04). 37 CFR 1.68 states that written declarations used in lieu of an oath "must set forth in the body of the declaration that all statements made

of the declarant's own knowledge are true **and** that all statements made on information and belief are believed to be true." However, in the interest of compact prosecution, the examiner has set forth below the extent to which the Declaration would have been found persuasive had it contained all statements required by 37 CFR 1.68 (see discussion following the enablement rejection set forth below).

Claim Rejections - 35 USC § 112

6. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons stated in the Office action of February 13, 2003, which reasons are repeated below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (MPEP 2164.01(a)).

Claims 8, 10, and 11 are drawn to methods of "diagnosing risk of HPV-induced neoplasia by detecting HPV-induced cell transformation in a patient infected with HPV"

(claim 8), methods of "diagnosing stage of HPV-induced disease in a patient infected with HPV" (claim 10), and methods of "diagnosing HPV-induced cancer in a patient infected with HPV" (claim 11). In these methods, the ratio of E6 and/or E7 mRNA level to L1 and/or L2 and/or E2 mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV-induced cell transformation and risk of neoplasia" (claim 8) or "early stage HPV-induced disease" (claim 10), while a ratio of greater than 4 is indicative of "HPV-induced cancer" (claim 11). Claims 9 and 12 are drawn to methods "of diagnosing the onset of HPV-induced disease in a patient infected with HPV" (claim 9) and methods "of diagnosing the risk or onset of HPV-induced cancer in a patient infected with HPV" (claim 12). In these methods, the ratio of group I mRNA level to group II and/or group III mRNA level is determined, and a ratio of greater than 2 is indicative of "HPV-induced neoplastic onset" (claim 9), while a ratio of greater than 4 is indicative of "high risk or onset of HPV-induced cancer" (claim 12). The specification indicates that group I genes include E6, E7, and E6 + E7, that group II genes include L1, L2, E4, and combinations thereof, and that group III includes E1, E2, E5, and combinations thereof (specification p. 10).

The specification exemplifies quantitation of HPV mRNA in different cultured cell lines (Example 1-2, Example 4). Cell lines examined include HaCaT cells, SiHa cells, and W12 cells. The specification teaches that HaCaT cells are an "immortalized human keratinocyte cell line" comprising approximately 1 episomal copy of HPV16 for every 40 cells, and states that "These cells are considered a representative of early stage infection or CIN I (cervical intraepithelial neoplasia)" (p. 22-23). The specification

teaches that SiHa cells are a "human cancer cell line" containing "1-2 copies of HPV16 integrated into the genome", and states that "These cells are considered to represent cancer" (p. 22-23). The specification teaches that W12 cells are a "non-tumorigenic human cervical keratinocyte cell line" that "contain approximately 100 copies of episomal HPV16 DNA and represent pre-malignant, immortalized cells or CIN II or CIN III" (p. 22-23).

The teachings of the specification show that the HPV16 (E6+E7)/L1 mRNA ratio is 0.68 for "early stage infection" HaCaT cells, 4.00 for "pre-malignant, immortalized" W12 cells, and "infinitely large" for "malignant" SiHa cells (p. 24, Table 2). Thus, based on the teachings of the specification, it appears that one of skill in the art could distinguish these three cell culture models of infection from one another by determining the HPV16 (E6+E7)/L1 gene transcript ratio. While the specification indicates that other ratios of HPV16 gene transcripts were measured and calculated for W12 and SiHa cells, no other data is presented for HaCaT cells (Table 2). Thus, based on the data presented by Applicant, it is not known what HPV16 mRNA ratios exist in HaCaT cells for transcript combinations other than (E6+E7)/L1. However, with respect to W12 and SiHa cells, Applicant further demonstrates that these two cell types have different HPV16 mRNA ratios for 5 other transcript combinations (see Table 2).

It is unpredictable as to whether one of skill in the art could practice the claimed invention. While the instant claims are directed to methods of, e.g., diagnosing cancer, cancer risk, or neoplastic onset in a patient, the specification does not provide evidence that the HPV gene transcript ratios set forth in the claims are associated with

transformation, cancer, disease stage, etc., in a patient. The data presented in the specification are limited to HPV16 transcript ratios in different types of cultured cell models, as discussed above. It is also noted that Applicants have not provided any type of declaratory evidence that establishes the validity of the various types of cultured cells employed in the specification as disease models, as was provided in parent application 09/210,168. Accordingly, in view of the lack of guidance provided in the specification, one must rely on the teachings of the prior art to provide further guidance and enablement of the methods of claims 8-12. The prior art is silent with respect to a correlation or correspondence between HPV gene transcript ratios measured in the 3 particular cell culture models employed by applicants and ratios measured in, e.g., different types of tissues samples taken from patients. Accordingly, neither the specification nor the art provide evidence that ratios measured in the 3 cell types employed by applicants are predictive of results that would be obtained in assaying patient tissues. The prior art as exemplified by Stoler et al (Human Pathology 23(2):117-128 [2/1992]) does suggest that expression of HPV E6 and E7 genes is elevated in some types of cancers (see entire reference). For example, Stoler et al demonstrate that, in high-grade squamous intraepithelial lesions associated with HPV-16, "signals from the E6-E7 ORFs were equal to or higher than from those from the E4-E5 region", whereas in low-grade squamous intraepithelial lesions, "Probes for transcripts spanning the E4-E5 ORFs yielded the most intense signals" (p. 119). However, the claimed invention is limited to the detection of particular ratios of mRNA levels to accomplish diagnosis, and the prior art, as exemplified by Stoler et al, does not

provide evidence that detection of the particular transcript ratios required by the instant claims would allow diagnosis in a patient of cancer, cancer risk, cancer stage, neoplastic onset, etc. Stoler et al also teach that the types and quantities of HPV transcripts expressed in patients will vary depending on cancer type, HPV type, and cell/tissue location (p. 119-120). Stoler et al further teach that HPV types 6 and 11, 16, and 18 are associated with different disease types (p. 117), and it is well known to those of skill in the art that different HPV types are associated with different disease types and cause diseases of varying severity. Thus, neither the specification nor the teachings of the prior art establish a correspondence or correlation between the particular ratios of HPV transcripts recited in the instant claims and "HPV-induced cell transformation" or risk for/onset of/stage of HPV-induced cancer in a patient. As it is unknown as to whether such a correspondence or correlation exists, it is unpredictable as to whether any quantity of experimentation would be sufficient to allow one of skill in the art to use the claimed invention. Further, based on the teachings of the specification and of the prior art, it is not only unpredictable as to whether the transcript ratios observed by Applicants in cultured cells might correlate with ratios in a patient, but to what types of HPVs and what types of cancers said ratios might be relevant. The data provided in the specification is limited to HPV16, and the prior art as exemplified by Stoler et al establishes that different HPV types are associated with different disease types. Accordingly, even if it were to be established that, e.g., the cultured cell models employed by Applicants in assaying HPV16 were valid models of HPV16-associated disease in patients, it is unpredictable, based on the guidance provided in the

specification and in the art, as to whether detection of such ratios in patients would be useful in diagnosis of disease caused by other HPV types. In view of the lack of guidance in the specification and in the prior art with respect to diagnosis and/or monitoring of cancer in a patient by determination of the HPV gene transcript ratios of the claims, including HPV16 gene transcript ratios, it would require undue experimentation to use the claimed invention.

7. **The response traverses the rejection on several grounds**.

First, the response states that pages 9-12 of the specification "generally describe how ratios of HPV genes are related to HPV-associated disease states," and particularly notes that the second paragraph of page 10 "provides guidelines as to HPV gene ratios that correspond to HPV-based disease states." The response states that "Table 1 on page 9 describes the expected level of HPV genes" and argues that "From reading Table 1 and Table 2, one skilled in the art understands that in low grade CIN (CIN1) tissues, HPV genes, such as E6, E7, E2, E4, L1, and L2, may not be detectable, i.e., a ratio value less than 2." Applicant asserts that "the ratios of other HPV gene combinations for W12 and SiHa cells in Table 2 other than (E6 + E7)/L1 and the specification together enable one skilled in the art to diagnose HPV-associated diseases." The response urges that "The Examples further describe how to practice the claimed invention using HPV 16 as an example," and particularly that "Example 1 describes how to detect and analyze nucleic acids, while Example 2 illustrates how to measure HPV mRNA, including but not limited to, E6/E7" and "Examples 3 and 4 describe quantitation of HPV 16 mRNA in cells of varying stages of infection and

malignancy." The response argues that "Specific working examples of all possible combinations need not be shown if one skilled in the art understands how to make and use the invention as described" and that "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art would be able to practice it without an undue amount of experimentation," citing MPEP 2164.02 and *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

These arguments have been thoroughly considered but are not persuasive. While the specification does recite relative levels of gene expression (see, e.g., Table 1) and ratios (p. 10) that are asserted to be indicative of disease stage, the specification provides no patient data to support these assertions. While the response states that Applicant's examples "describe how to practice the claimed invention," this is not in fact the case, as the claimed invention is drawn to methods performed on patient samples, while the Examples describe methods practiced on cultured cells. It was acknowledged in the prior Office action that the specification would enable one to differentiate the various cell culture models exemplified in the specification based on HPV 16 gene transcript ratios; however, the claims are not directed to such an invention, but rather to methods practiced on patient samples. Thus, while it is further acknowledged that working examples of "all possible combinations" of an invention (or even most combinations of an invention) are not required, in the instant case the specification does not provide any working examples of the invention claimed (i.e., of a method practiced on patient samples). Additionally, as discussed in the prior Office action, neither the specification nor the prior art establishes a correlation or correspondence between HPV

transcript ratios in the 3 cell culture models employed by Applicant and ratios measured in patient samples. As Applicant's Declaration cannot be considered, it cannot be relied upon to establish the validity of the cultured cells as disease models. Accordingly, as it is completely unpredictable as to whether detection of the ratios of the claims in patients would actually correlate with disease/disease stages, the quantity of experimentation required to practice the claimed invention is undue. With further regard to Applicant's examples, it is also noted that not only are the examples limited to assays performed on cultured cells, but they are further limited to a single HPV type (HPV 16). The specification does not provide evidence that these ratios are applicable to other strains of HPV, and it is again noted that the prior art as exemplified by Stoler et al that the types and quantities of HPV transcripts expressed in patients vary depending on cancer type, HPV type, and cell/tissue location (p. 119-120). Accordingly, absent evidence that HPV types other than HPV 16 actually exhibit the same or similar ratios of gene transcripts, either in cultured cells or in patients, as those reported by Applicants for HPV 16 in cultured cells, it is unpredictable as to whether this would be case. For these reasons, Applicant's arguments are not persuasive.

Next, the response presents several arguments that rely on information and data provided in the Declaration under 37 CFR 1.132 filed with Applicant's response. However, as the Declaration cannot be considered (for the reasons stated above), it cannot be relied upon in an attempt to overcome the instant rejection. Arguments reliant on Applicant's Declaration include those related to the asserted correlation of the cell line models in the specification with particular HPV-induced disease stages (pages

9 and 10), as well as those related to the association of various HPV types with many different cancers (page 10) and evidence related to mRNA ratios for HPV 18 and HPV 31 in cultured cells (page 10). While the Declaration cannot be relied upon, it is again noted that extent to which the Declaration would be persuasive if it were not defective is discussed below. The response further argues that "A patient infected or suspected of infection with human papillomavirus is not any type of patient" and urges that "with respect to 'a patient infected with HPV," the claims are "fully enabled." However, while it is acknowledged that a "patient infected or suspected of infection with human papillomavirus" is not in fact any type of patient, it is again noted that the specification does not provide data obtained with any type of patient. The specification is not enabling with respect to such patients, for the reasons discussed in the prior Office action and above. The response also points to teachings in the specification and in the zur Hausen reference that many different HPV types are associated with cancer. While this is acknowledged, the fact that many HPV types are associated with cancer does not mean that these various HPV types cause cancer in a manner identical to HPV 16, or that the ratios of different transcripts present during different stages of cancer types caused by different HPV types will be the same as those present during HPV 16-induced cancer. The instant claims require the use of particular transcript ratios in diagnosis, and thus enablement of the claims would require not just evidence that various HPV types cause cancer (as many are certainly known to do), but rather evidence that the particular ratios recited in the claims are actually relevant when diagnosing cancer caused by HPV 16 or another HPV type or types. In the instant

case, neither the specification nor the prior art establishes that the ratios of the claims are relevant when diagnosing HPV-16 induced cancer in a patient, or cancer induced by any other HPV type in a patient. Further, neither the specification nor the art teaches that the ratios observed in patients at particular stages of HPV-induced cancer correlate with or correspond to the ratios observed at the corresponding stages in cancer or cancers caused by another HPV type. Accordingly, Applicant's arguments are not persuasive.

Finally, the response disputes the examiner's contention that "the prior art is silent with respect to a correlation between HPV gene transcript ratios and disease." The response points to the Stoler et al reference cited by the examiner, noting that the examiner has admitted that Stoler et al "demonstrate that HPV E6 and E7 genes have elevated expression." The response further argues that "although the types of HPV are associated with different diseases, the instant specification enables one skilled in the art to assess the disease stage and/or risk from measuring HPV gene transcripts, and more particularly, the HPV gene transcript ratios." These arguments have been thoroughly considered but are not convincing. First, the instant claims are not drawn to methods that merely require the detection of elevated E6 and/or E7, but rather to methods in which diagnosis relies on the ratio of E6/E7 to other gene transcripts. Accordingly, the mere fact that E6/E7 expression was known to be elevated (as was clearly known at the time the instant invention was made) does not enable an invention in which particular transcript ratios are diagnostic; enablement of the claimed invention would require, e.g., evidence that particular ratios of transcripts in fact correlate with

particular conditions or disease stages in patients. Further, while it is possible that different HPV-induced diseases do exhibit, e.g., particular expression patterns or ratios that are indicative of various disease stages, this possibility is merely speculative; actual evidence would be required to establish that this is in fact the case. Further, it is completely unpredictable as to whether the ratios of gene transcripts observed in HPV 16-induced disease would be the same or different as those observed in other HPV types. Accordingly, Applicant's arguments are not convincing.

As Applicant's arguments are not persuasive for all the reasons given above, this rejection is maintained.

8. Regarding the Declaration under 37 C.F.R. 1.132 filed June 13, 2003, it is again noted that the declaration is defective and therefore cannot be considered. However, had the Declaration not been defective, it would have been persuasive in part, as discussed below.

Applicant has established via the Declaration that HaCaT cells infected by the procedure of White et al are considered by those of skill in the art to be a model for early stage HPV16 infection (see, e.g., p. 3 of the Declaration and p. 962 of White et al), that W12 cells (containing approximately 100 episomal copies of HPV16 DNA) are considered by those of skill in the art to be a model for low grade HPV16 induced lesions (see, e.g., p. 4 of the Declaration and p. 855 of Rong et al), and that SiHa cells (containing one integrated copy of HPV16 DNA) are considered to be a model for high grade HPV16-induced lesions (see, e.g., p. 4 of the Declaration and p. 855 of Rong et al). Accordingly, Applicant's Declaration establishes enablement of the claims in part,

specifically, to the extent that the claims are drawn to diagnosis of HPV16-induced cancer and stages thereof by detecting in patients the ratios encompassed by the instant claims. However, the present claims are not limited to such methods, but rather encompass any HPV type. While the Declaration does cite teachings in the art that E6 and E7 expression are associated with malignant transformation in cancers induced by other HPV types (citing, e.g., Koromilas et al and Goodwin and DiMaio), such teachings are insufficient to establish that the transcript ratios of the instant claims relate to particular types or stages of disease. Rather, such teachings (like those of Stoler et al, discussed above), merely establish the fact that E6/E7 expression is often elevated in HPV-induced cancers. It is again noted that Stoler et al teach that the types and quantities of HPV transcripts expressed in patients vary depending on cancer type, HPV type, and cell/tissue location (p. 119-120). While Applicant's Declaration does establish a correlation between human disease and cultured cells comprising HPV16 nucleic acids, none of the cited references refute the teachings of the art exemplified by Stoler et al, which suggest that it is unpredictable as to whether ratios associated with HPV16-induced disease would be associated with disease induced by other types of HPV.

The Declaration also states Declarant's opinion that the claims are enabled, which opinion is supported by data and findings of E6-E7/L1 transcript ratios for HPV 18 in HeLa cells (pages 7-9) and HPV 31 in LKP31 and A31 cells (pages 9-11). Declarant reports an E6-E7/L1 mRNA ratio of 9.5 for HeLa cells (an HPV 18 positive human cervical carcinoma cell line), and states that "This E6-E7/L1 mRNA ratio correlates to the claimed invention, i.e. This ratio represents substantially higher expression of the

carcinogenesis-related genes E6-E7 than the viral capsid structural L1 gene." Regarding data obtained with HPV 31, Declarant states that "Both cell lines utilized....LKP31 and A31, contained episomal and integrated copies of HPV 31 DNA; however, LKP31 had a higher copy number than A31, and thus LKP31 is assumed to represent a cell line that is closer to cancer" (see page 10). Declarant reports an E6-E7/L1 ratio of 11.7 for the LKP31 cell line and 8.4 for the A31 cell line, stating that "The E6-E7/L1 mRNA ratio was found to be above 2 for both HPV 31 positive cell lines" and that "The levels of E6-E7 and L1 mRNA were approximately 2-fold higher in LKP31 cells than in the A31 cells." Declarant further states that "The higher level of E6-E7 to L1 is expected in cells that are transformed by HPV 31 to the pre-malignant state, and as expected, the more neoplastic cell line LKP31 has a higher ratio," and concludes that "These experiments demonstrate that HPV gene transcript ratios of different HPV types, i.e., HPV 18 and HPV 31, may be used to determine the disease level in cell model systems of HPV-infected cells."

Declarant's opinions and data obtained with HPV 18 and HPV 31 are not persuasive with respect to enablement of the invention of the instant claims. First, it is noted that while the instant claims are limited to diagnostic methods employing patient samples, the data reported by Declarant was obtained with cultured cells. While, as discussed above, the Declaration does establish the validity of the 3 cell lines exemplified in the specification as models of various HPV 16-induced disease stages, neither the specification, the Declaration, nor the prior art establish a correlation between transcript ratios in HeLa cells and patients with a particular stage of HPV 18

induced disease, or between transcript ratios in LKP31 and/or A31 cells and patients with particular stages of HPV 31-induced disease. With further regard to HPV 18, the Declaration does not indicate with which of the three types/stages of disease disclosed in the specification the HeLa cell model is believed to correlate, or provide evidence of such a correlation. Thus, while the Declaration does provide evidence of a ratio of 9.5 for HeLa cells, it is unpredictable whether such a ratio might also be identified in a patient sample, and if detected, with what disease stage this ratio would correlate. With further regard to HPV 31, the Declaration similarly does not indicate with which of the three types/stages of disease disclosed in the specification the LKP31 and A31 cell models are believed to correlate. While Declarant does indicate that LKP31 is "assumed to represent a cell line that is closer to cancer" due to its higher HPV 31 copy number, the Declaration does not indicate whether one or both of these cell lines represents cancer, a pre-malignancy, etc. It is further noted that these two cell lines are disclosed to be structurally different from the HPV 16 models of the specification; specifically, while both LKP31 and A31 contain both episomal and integrated copies of HPV 31 DNA, the SiHa cells of the specification contain 1-2 copies of integrated HPV 16 DNA and are disclosed to "represent cancer," while the W12 cells of the specification contain "approximately 100 copies of episomal HPV16 DNA" and are disclosed to represent "pre-malignant, immortalized cells or CIN II or CIN III." It is not apparent how or whether the LKP31 and A31 models relate either to different stages of HPV 31 induced disease, or to the HPV 16 models of the specification. While the Declaration does provide evidence of a ratio of 11.7 for LKP31 cells and of 8.4 for A31 cells, it is

unpredictable whether such ratios might also be identified in a patient sample, and if detected, with what disease stage or stages these ratios would correlate. Finally, it is noted that while Declarant states that "HPV gene transcript ratios of different HPV types, i.e., HPV 18 and HPV 31, may be used to determine the disease level in cell model systems of HPV-infected cells," the instant claims are not drawn to the determination of disease levels in cell model systems, but the diagnosis of disease and disease stages in patients. The Declaration, considered in combination with the other evidence available to the examiner (including the teachings of the specification and of the prior art), is ineffective to establish enablement of the claimed invention with respect to HPV 18, HPV 31, or other HPV types other than HPV 16 at the time the invention was made.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 8-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, respectively, of U.S. Patent No. 6,355,424B1, for the reasons given in the Office action of February 13, 2003 (which reasons are repeated below). An obviousness type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). In the instant case, although the conflicting claims are not identical, they are not patentably distinct from each other because claims 8-12 of the instant application are generic to all that is recited in claims 1-5, respectively, of the '424 patent. That is, claims 1-5 of the '424 patent fall entirely within the scope of claims 8-12, respectively, or, in other words, claims 8-12 are anticipated by claims 1-5, respectively. Specifically, instant claims 8-12 are generic to any type of HPV, including HPV16, the species that is recited in claims 1-5 of the '424 patent. Thus, claims 1-5 of the '424 patent anticipate instant claims 8-12, respectively.

It is noted that in response to a Notice of Non-Responsive Amendment mailed September 22, 2003, Applicant filed a Response on October 22, 2003 in which Applicant agreed to file a terminal disclaimer once claims 8-12 are in condition for allowance but for the double patenting rejection. As a terminal disclaimer has yet to be filed, this rejection is maintained.

Drawings

11. It is noted that Figure 7 as filed on June 13, 2003 is plain and legible and is therefore approved. Figures 1-6 were previously approved as filed on October 4, 2001.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Patent Examiner
April 15, 2004